QUININE

A PHYSIOLOGICAL ANTIDOTE

TO THE

MALARIAL POISON.

BY

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QUININE A PHYSIOLOGICAL ANTIDOTE TO THE MALARIAL POISON,

THE most important and ancient of the uses of quinine depends, undoubtedly, on the power it has over malarial diseases, both as a prophylactic and curative agent,—a power which has not as yet been explained by our knowledge of its physiological action, but which is so evident, that by many it is considered a specific for these diseases. That it is not a specific we need hardly say, unless the term may be applied to a remedy whose power we know, but of whose mode of action we are ignorant, because it does not always act as a prophylactic when taken as a preventative, nor is it always curative, which would not be the case were it a true specific.

But so interesting a problem as the action of quinine in these diseases has naturally brought forward several theories to explain its action. The theory of its specific action hardly deserves the name of such on account of its improbability; other theories, however, have been adduced of a much more plausible and rational character.

Thus, Piorry, Mosler, and others explain the influence of quinine by an action on the enlarged spleen, viz., that the effect it produces upon the fever is in proportion to the reduction of the spleen; that the disease is cured simultaneously with the subsidence of the splenic enlargement; and that the fever is apt to recur as long as the spleen exceeds its normal size. This enlargement or engorgement of the spleen and other organs is, however, only a secondary phenomenon, and is a result, and not the *origo mali*, as Piorry and his followers assert, who declare the spleen to be the primary seat of the disease. Thus, according to Jacquot, Saurier, and others, people are said to die of malarial fever in Africa without the slightest swelling of the spleen. A singular case is also related, in which a man received an extensive wound of the wall of the abdomen on the left side, through which the spleen escaped; as it could not be returned it had to be removed.[1] The patient recovered from the operation, and had malarial fever afterwards, just the same as before, although eventually a post-

[1] Ziemssen, vol. ii. p. 645.

mortem examination showed nothing but the shrivelled rudiment of spleen left.

Besides, M. Piorry's assertion as to the diminution of the size of the spleen after a dose of quinine has been disproved by many careful observers, and other investigators have failed in their attempts to reduce the size of the spleen in dogs by giving quinine, as Kuchenmeister and Mosler declare they did ; so that, even granting the enlarged spleen to be the cause of the disease, the action of quinine in immediately diminishing its size remains to be proved, or rather has been disproved. Besides, in some cases of these diseases, the spleen is not enlarged, and yet they are cured with quinine ; and in others the fever disappears before the enlarged spleen is reduced in size. Hence at the present day M. Piorry's theory is generally held to be untenable, as it is founded on false premises.

Then Binz advanced his theory, taking first for granted the germ theory of malarial poisoning, and arguing from the effects of quinine on the white blood-corpuscles, that in malarial fever it acts as an irritant to those germ cells, and so renders them incapable of further development, and thus arrests and cures the disease ; and by its action on the white corpuscles destroying them, it diminishes their number, diminishes the functional activity of the spleen, and as a result the organ diminishes in size.

But this theory is based, as it appears to us, upon rather an unstable basis. First, because Binz takes for granted that quinine acts on the white corpuscles in the body as it does out of the body, his experiments not being received as at all conclusive on this point. Besides, the action of quinine in checking the movements of the white corpuscles is much more probably the result of an action on the walls of the capillary vessels, causing them to contract, than on the corpuscles themselves. As, no doubt, in relaxation of the capillaries approaching stasis the white corpuscles pass readily through the walls of the vessels, and by increasing arterial tension, this is prevented.

For this reason Harley is strongly of opinion that the beneficial influence of quinine in ague, and the removal of the splenic swelling, must be attributed to this effect on the bloodvessels by which the congestion is relieved, rather than to a restraining influence on the movements of the white corpuscles or leucocytes, as they have been termed. Harley's theory is certainly more probable than that of Professor Binz, because, as he says, if the white corpuscles were a species of entozoa, capable of an independent existence like the infusoria, then a direct action of quinine might be possible. But as we have already seen—however desirable it may be to reduce the splenic enlargement—it is not the cause of the disease, and hence treatment directed with this view does not relieve the symptoms of the fever, although it may benefit the local complication. Nor is it apparent that arterial relaxation

is more marked in malarial than in other fevers, by modifying which relief from the symptoms might be expected.

Secondly, he takes for granted, what is still unsettled, the germ theory of malarial poisoning. Thirdly, that on this hypothetical poison quinine must act as it does on some other germs, or on the white blood-corpuscles. That, in fact, quinine is a chemical antidote to the malarial poison. But its effects on these diseases do not support this idea, as we shall immediately see. As to its action on the spleen, that is of little consequence, as, of course, if the theory fails in the first part, its mode of action in regard to the enlarged spleen must also fall to the ground. All the more so, as we have already seen that the beneficial effects of quinine in these diseases are not the result of an action on the spleen. Hence neither the theory of M. Piorry, of Professor Binz, nor of Dr Harley is sufficient to account for the good results which follow the administration of quinine in malarial poisoning.

But by noting the symptoms of malarial fever and the clinical experience of its treatment with quinine and other remedies, and by examining the action of quinine and other remedies on the nervous system, we might, we think, get some further light on its action rather than by confining our attenti on merely to the more common manifestations of its physiological action.

For, by noting the results of treatment, we are often able to explain the action of remedies in the same way as a knowledge of the action of some remedies in disease has assisted us to a better understanding of the nature of these diseases. So, on the other hand, there is no reason to doubt but that a knowledge of disease and the effects of remedies will often throw light on their physiological action, and explain the *modus operandi* of their curative power, which is not always apparent from their action in health.

When quinine is administered in malarial fever, the beneficial effects which follow cannot be due to its having the power of eliminating the poison from the system, as it has no evacuant action by skin, bowels, or kidneys. Nor is there any evidence that the symptoms of malarial fever are due to structnral changes of any organ, as the spleen, by acting on which quinine might prove curative.

It must therefore act in the system either on the paludal poison itself, by destroying it or paralyzing its power, or by an antagonistic action on the (nervous) system, protect it from the shock of the poison, and so prevent or modify those symptoms which are the usual manifestations of the disease. That is to say, quinine must be either a chemical or a physiological antidote ; in the one case, the poison itself is attacked by the remedy ; in the other, the system, at least that part of it which is the seat of selection by the poison, is braced up, so as to resist its power in whole or in part, according to circumstances.

That malaria is a poison cannot be doubted, although of its

precise nature we are ignorant, and which, by entering the blood, gives rise to certain defined and well-marked symptoms.

The first of these two theories, viz., that of its being a chemical antidote, is almost analogous to that of Professor Binz, and of which we have already seen there is not sufficient proof. Still, the fact of quinine being a chemical antidote, might remain, although Professor Binz's theory be untenable, as it is, more properly speaking, simply an explanation of its action as a chemical antidote. Hence additional proof is required to refute the idea of its being a chemical antidote in any way.

This idea of its antidotal power appears to be in considerable favour with Stillé, who says,[1]—"Admitting that a morbid element in the blood is the immediate cause of the paroxysms of periodical fever, some such cure appears to be most consistent with probability." That it is not most consistent with probability we will endeavour to show, and also that the theory of its being a physiological antidote is the most consistent with probability, as we, like Stillé, believe that the effects of quinine can only be explained by the supposition that quinine eliminates, destroys, or renders inert or inoperative some noxious principle contained in the blood. A strong argument against its power as a chemical antidote is, that it, and other antiseptics, as carbolic and sulphurous acids, which have been given to cut short or prevent diseases, the result of a poison in the blood, have failed.

Thus carbolic acid, which is a powerful antiseptic outside the body, when administered in such diseases as scarlet fever, smallpox, and relapsing fever, in which diseases a poison is undoubtedly present in the blood, does not possess any antidotal power, the nature even of the poison having been demonstrated in the case of smallpox and relapsing fever. Besides, in the recently published results of Dr J. V. Laborde's experiments on the preventative and curative action of reputed antiseptics, he found in contradiction to the statement of Binz, that quinine, when injected in septicæmia, even in the highest doses compatible with life, neither acted as a preventative to the development of the disease, nor averted it when it was produced. And there is no reason to believe that quinine has any more affinity for the malarial poison than it has for the poison of these other diseases; and clinical experience supports this.

Thus, in malarial fever, although quinine arrests the attacks in some, in others it only diminishes their intensity, and sometimes even fails entirely, and always requires to be repeated. This is decidedly against its antiseptic or chemical action; because it is not possible to believe in the power of a chemical antidote which requires to be so frequently repeated as quinine so often has to be, and which sometimes fails, or in a poison which proves itself so speedily active after its apparent destruction, so as to be able to reproduce all its former effects on the economy in

[1] Stillé's *Therapeutics*, vol. i. p. 465.

so short a time, even after complete removal from the infected district, and when no new infection is possible. Indeed, the frequency with which quinine requires to be given, and the duration of the disease, notwithstanding its repeated administration, are all insurmountable difficulties in the way of accepting the theory of the chemical action of quinine on the malarial poison, more especially as the secondary lesions are not the cause of the periodical attacks. These paroxysms are, perhaps, the result of a somewhat similar process to what Heydenreich has shown to be the cause of the relapses in relapsing fever, viz., fresh crops of the germs (spirillæ), being cotemporaneous with the fever paroxysms.

That the poison of malaria must have the power of continuing or reproducing itself in the blood is highly probable, both from the duration of the disease and the periodical paroxysms. And if you suppose that quinine arrests a paroxysm by its chemical action on the poison, how is it possible to reconcile this with their continued recurrence after its repeated administration, and is so far antagonistic to the germ theory of malarial infection, *i.e.*, if quinine is capable of, as Binz asserts, paralyzing the irritant miasm by virtue of its antiseptic power, or rendering the germs incapable of further development? And certainly there is much more evidence to support the opinion of malarial fever being due to the presence of a poison in the blood, than there is in support of the theory of Binz as to the action of quinine. This word paralyzing is, however, rather vague, and perhaps is meant to be an apology for the recurrence of the fever paroxysms, and to signify that quinine does not always destroy, but only paralyzes for a time the obnoxious germs.

Surely this expresses a want of confidence in the theory, because, after arresting the antiseptic and fatal influence of quinine on such like germs outside the body, Binz argues from that a similar action within the body; and yet, if this be true, why does quinine modify what is a fatal action in the one case to a paralyzing one in the other, and where is the proof of it? Hence the theory of quinine being a chemical antidote or counter poison to the malarial poison appears simply untenable, and in the same category we may place the theory of Professor Binz.

The second theory, that of quinine being a physiological antidote, remains to be examined, viz., that by an action on certain parts of the nervous system it diminishes the shock, and thus either prevents or modifies the symptoms which are the manifestations of the action of the malarial poison on these parts. That the nervous system is, in the first place, the principal seat of selection of the poison, is generally allowed, both from many of the symptoms of the disease pointing strongly to a direct influence of the malarial poison on the nervous system, and also from the result of treatment, viz., that treatment directed upon this belief is the most powerful in ameliorating the symptoms or curing the disease.

Perhaps, as some believe, an excito-caloric centre is disturbed, whereby intermissions and remissions are produced.

This idea of an action on the nervous system is compatible with the need of repeating the remedy,—which, as we have seen, Binz's theory is not,—as the stimulus of quinine and of all other stimuli to the nervous system can only last a certain and limited time, depending on the dose and condition of the patient's health, and whether, as in the case of intermittent fever, there is any antagonistic or depressing influence at work. It is not only compatible with repeating the doses, but demands their repetition until the poison is exhausted, or dies a natural death, as there is no indication of its being eliminated. From this follows the approved method of administering the remedy. It also explains, what by any other theory is inexplicable, why quinine is sometimes unsuccessful and not always equally beneficial. These results being undoubtedly due to different causes—to the dose being too small, the use of bad preparations, the varying susceptibilities of patient to the action of the remedy, as is the case with the action of most powerful remedies, and also to the difference in the action and power of the poison in different constitutions and temperaments, the duration of the disease, and the presence or absence of complications or secondary morbid conditions, or to the disease not being correctly diagnosed, and being wrongly attributed to malarial poisoning. Another plea in favour of this theory is, that our knowledge of its general physiological action does not explain its effect in malarial fever, unless, according to M. Seé, who ascribes its effects in "ague to its action on the heart, diminishing its force and frequency; to its action on the peripheral arteries, lowering their tension and producing dilatation; to its action on the spinal cord and vaso-motor centres, acting as a sedative and diminishing their excitability, and diminishing the temperature of the body." Yet, as he says, it cannot be regarded as a specific or counter-poison in the various forms of malarial fever, as it does not prevent malarial poisoning when taken as a prophylactic, it does not prevent recurrence after a variable period, and it is useless in some of the most fatal forms, especially when the fever tends to assume a continued type. And although this statement of M. Seé is neither quite accurate in regard to the physiological action of quinine, nor to its power as a prophylactic, it explains what we mean when we say that its action in these diseases cannot be deduced from any of its known physiological effects, as none of these appear in the smallest degree likely to counteract the action of the malarial poison on the system, if we compare the symptoms of the disease and the known physiological actions of quinine. Besides, we have other remedies which act more powerfully in these respects than quinine, and which yet have no curative action like quinine in malarial diseases, as they would have were M. Seé's theory correct. Hence, M. Seé evidently thinks that what, perhaps, no one action is capable of effecting, when combined the result is successful. No

doubt, the beneficial effects of quinine are due to its physiological actions, but certainly not to any one or all of those enumerated above.

But although, as we have said, the known physiological action of quinine does not apparently throw any light on the connexion between its action and the beneficial results which follow its administration in ague, do we know all its actions? Certainly not. If we do not know its action in intermittent fever, then how are we to discover it?

As every one knows, there are certain actions of remedies, especially on nerve structures, which it is impossible directly to demonstrate, but an action, of which indirectly very strong and even conclusive proof can be obtained by noting their effects; although this is much more difficult when we have to examine their actions in disease, and of which in health there may be little or no evidence. "Thus," Binz says, "we are ignorant of any direct relation between quinine and the nervous system which might be utilized for therapeutic purposes, although we cannot deny that such may exist. Any direct tonic influence exerted by quinine upon the nervous system is at present purely hypothetical, and unsupported by a single experiment." [1] This is, in fact, just what we might expect. You cannot prove by direct experiment what does not exist, viz., the action of quinine in ague on a healthy man or frog. The proof must be from the effects of its action in disease, *i.e.*, clinical experience; and in this way it is possible to get, we believe, as conclusive evidence as by direct experiment.

That quinine is a nervine tonic even Binz allows is probable. That it is, we think there is sufficient proof over and above its tonic action to the general nutrition by stimulating the digestive functions and retarding tissue metamorphosis. Because, in certain nervous derangements, it proves curative in virtue of this action, as it can be by no other, long before it could have time to improve the general nutrition, as in periodic neuralgia, asthma, laryngismus stridulus, rigors, etc., etc.

Its beneficial influence in those diseases which we know are due to a disturbance of enervation, must be due to an action on the nervous system. This is borne out by clinical experience, for quinine is beneficial in neuralgia, just in proportion as the cause is of purely nervous origin, and occurring in those in whom there is want of tone.

Stillé thus explains its action in periodic neuralgia, "by regulating and moderating the disorder of the nervous system," and then explains its action in intermittent fever, "by directly neutralizing a material poison, or causing elimination from the system." That it does not do the latter, we have already seen; as to its being a chemical antidote, clinical experience is against it: then, why not apply the explanation of its power in periodic neuralgia to its

[1] Binz's *Elements of Therapeutics*, p. 210.

influence over malarial fever? It is the most probable of the explanations, and the only one which clinical experience supports.

In all these nervous diseases there is good reason to believe, that not only is some part of the nervous system either primarily at fault, or the point of attack, but also that in some the whole nervous system is in an atonic condition or unstrung, as they occur most frequently in those of weak constitution, whether this condition is hereditary or acquired. In others, the disease or symptoms are the result of a sudden shock, which suddenly and for a time only reduces the nervous tension and brings it below par.

Take, for instance, the rigor, etc., which frequently follows catheterization. This is undoubtedly due to an impression or shock to the nervous system, and which can be prevented or checked by a dose of quinine. The action of quinine on the nervous system is therefore here as evident and undoubted, as that the rigor is the result of functional disturbance of the nervous system, the one mutually proving the other.

Quinine can, therefore, arrest other rigors and fever paroxysms than those which occur in intermittent fever, and that without there being any suspicion of the presence of a poison in the blood. But, no doubt, poisons in the blood, by acting directly on the nervous system, can disturb it even more readily and directly than the presence of a foreign body in the urethra. Still, there is no reason to prevent quinine acting in the one case as in the other; only in the case of a poison in the blood, like the malarial, the quinine must be repeated, if these shocks or periodical attacks are to be prevented, until the poison has exhausted itself. The greater powers of quinine in malarial fever than in other fevers can readily be accounted for by not only the blood poison being of a different nature, but chiefly by the different seat of selection of these poisons. Whenever in disease, however, the symptoms of the attack approach the type of malarial fever, then quinine is beneficial; that is, when that portion of the nervous system or part of it is involved which is always implicated in malarial poisoning. So that we have proof that quinine exerts the same action in other diseases besides those of a malarial origin, which is against the chemical action of the drug, and, from the nature of the cases in which it proves useful, is strongly corroborative of a tonic action on certain parts of the nervous system, and therefore of its being antagonistic to the action of the malarial poison as a physiological antidote.

In health this action of quinine is, however, not very manifest. But the symptoms of cinchonism, headache, buzzing in the ear, confusion of sight, etc., point undoubtedly to an action on the brain; and that not only does it act on the brain, we may readily infer from its other effects, just as alcohol acts as a stimulant or sedative to other parts of the nervous system in addition to the brain. The cerebral effects are, however, the most prominent, as they are most

clearly and quickly evident from its delicate functions being so readily disturbed.

And although this beneficial action of quinine is not usually apparent until some time after the symptoms of cinchonism have disappeared, that is, until it has prevented or diminished the next paroxysm of the disease, it does not by any means follow that therefore the curative power of quinine cannot be due to a stimulating or sedative action, because those sensible effects have ceased; unless it were held, which it is not, that the malarial poison acted principally on the brain, or that, with the disappearance of these most prominent effects, all the other actions of the drug ceased. It simply shows that certain of its cerebral effects have diminished, just as with alcohol, which first excites, and then acts as a sedative, when the excitant effects pass off, or are merged into other symptoms, we cannot say that alcohol has ceased to act; and even when all cerebral symptoms disappear, its stimulant action lingers in other parts until it is entirely eliminated from the system. It is also possible to understand that the beneficial result of this stimulant action may be shown after elimination of the stimulant.

For instance, if by a dose of quinine the next attack of fever which would naturally occur twenty-four or forty-eight hours afterwards is prevented, it does not follow that quinine waits on the paroxysms and then attacks it. The beneficial action commences as soon as it is absorbed, and by its action on the nervous system the paroxysm is prevented not by an action twenty-four hours after administration, but by its immediate action preventing that disturbance, which in time develops into a fever paroxysm. So that we must not always take for granted that the most obvious effects of nervous action are the only ones produced by remedies, as an action that in health may not be manifest, may in case of functional derangement be actively remedial, which is the reason why certain curative actions of remedies are only witnessed in disease. Nor is this action peculiar to quinine. Compare, for instance, the effects of arsenic in chorea with what are ordinarily known as its physiological actions; and in regard to it the same may be said as is said by some of quinine and its action on malarial disease, viz., that its effect in chorea cannot be explained by its known or evident physiological action; yet no one can doubt that arsenic acts in chorea purely as a nervine tonic.

Another link in this chain of reasoning is, that other nervine stimulants, as arsenic, caffeine, alcohol, beberia, piperine, gentian, capsicum, strychnia, etc., although differing considerably both in kind and degree of active power, have some power over intermittent fever and other diseases of a nervous pathology. In fact, as adjuvants, and occasionally as substitutes, they are invaluable, as clinical experience has amply testified.

In virtue, however, of certain peculiar properties, one is more useful than another in different nervous diseases, due partly to their somewhat different actions, the part of the nervous system affected, and the cause of the disturbance. Thus, quinine appears to exert an influence on that part of the nervous system for which the malarial poison has a special affinity; and in virtue of this, is more curative than the other remedies, just as arsenic has a special tonic influence on the motor nerves, in virtue of which it is more powerful in chorea; and caffeine, an action on the pulmonary nerves, which renders it more useful in asthma. Hence we believe quinine to act in malarial disease as a stimulant or sedative to the nervous system, especially to that part most implicated in these diseases; and that it is principally in virtue of this action that it proves curative, by rendering the malarial poison inoperative by an antagonistic action on the nervous system, and that it proves beneficial in proportion as the nervous disturbance is predominant, and to the absence of complications. Although we arrive at this conclusion by argument, and not direct experiment, the evidence in its favour appears to us so strong as to give it the place of a more than probable theory, and to be a much more reasonable explanation of its action than any other as yet brought forward; and that by this method of reasoning it is possible to arrive at correct conclusions in absence of direct experience, the literature of therapeutics amply shows.

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